Treatment of Melanoma—Success or Failure?

LEWIS W. GUISS, *M.D.*, Los Angeles

• **The treatment of melanoma should be by radical surgical excision of the primary lesion and dissection of the regional nodes.**

Where possible this should be done in anatomic continuity; otherwise in physical discontinuity but at the same time.

If maximum salvage is to be achieved the nodal dissection must be effected before there is clinical evidence of involvement by metastasis.

Amputation of extremities should be reserved for cases in which there is evident metastasis between the original focus and the regional lymph node areas.

THE PROBLEM of definitive treatment of melanoma is complex. The factors that may contribute to success or failure are so many and various that any attempt at analysis is necessarily tenuous. Because of the unsatisfactory end results that have been achieved in the treatment of melanoma to date, considerable effort has been expended in analyzing a rather large series of cases. The emphasis has always been on consideration of factors that may or may not have contributed to successful management. Failures and deaths have been admitted but more or less disregarded as something unpleasant and even inevitable.

This discussion is a summary of an experience with the treatment of melanoma in private practice, with emphasis upon analysis of the failures, since the reasons for failure may be far more important than the reasons for success.

This report covers a consecutive series of 145 patients observed in private practice. Table 1 summarizes the clinical status of the patients at the time of their first visit. Of those who were then still eligible for definitive treatment, only 27 had had no treatment and no biopsy of the lesion, an additional seven had had biopsy, but no treatment and 47 had had definitive treatment of the primary lesion. Despite the fact that eight of these 81 patients already had disseminated metastasis, responsibility was accepted for their care and the 81 cases are regarded as the definitive group for analysis. Another 21 patients were not observed until after their treatment elsewhere was completed. They have been cared for since that time, but, since no responsibility for planning their care was involved, they are not included in the definitive group. The final 43 patients were seen in consultation only, almost invariably on a single occasion; while some responsibility is certainly accepted for their subsequent care, the author has not been in a position to follow their course and so has excluded them also from the definitive group.

From the Department of Surgery, School of Medicine, University of Southern California, Los Angeles.

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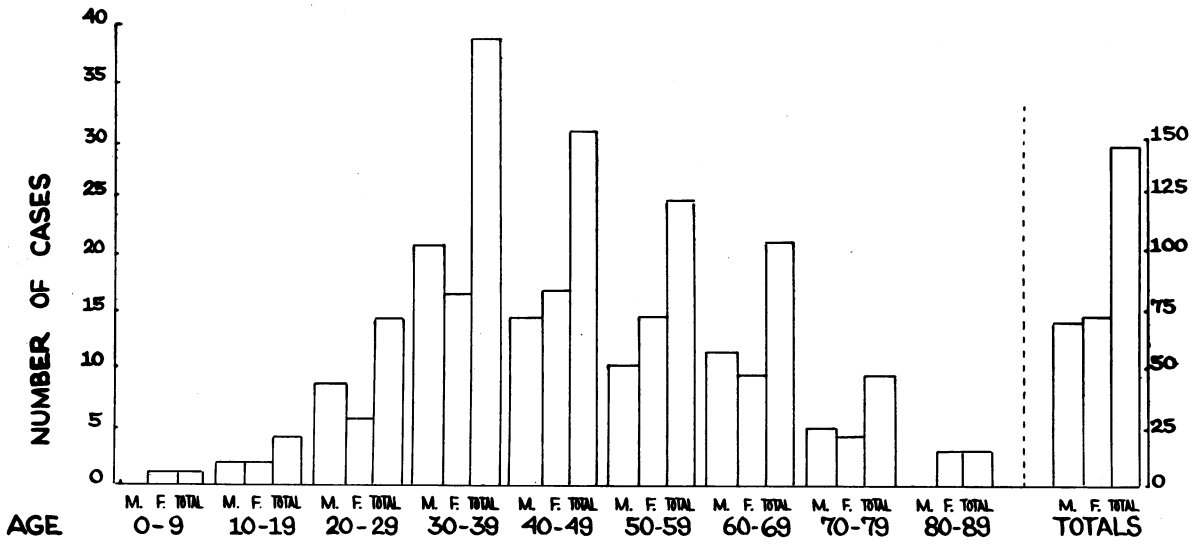

Chart 1.—Data on age and sex of patients with melanoma.

TABLE 1.—*Clinical Status of 145 Patients with Melanoma at Time of First Visit*

Previous Treatment	Totals	Stage of Disease: Limited to Primary	Metastasis to Regional Nodes	Disseminated Disease	Other
None	34*	23	7	4	....
Primary treated	47	35	8	4	....
Definitive treatment complete	21	....	....	7	14†
Consultation only	43	4	5	11	23†
	145	62	20	26	37†

*7 previously biopsied.
†Usually free of evident disease; a few with local recurrence.

Chart 1 gives the sex distribution of the total number of cases divided into decades, and is of interest only in demonstrating that melanoma is a disease primarily of early adult and middle age. Table 2 is an attempt to summarize the factor of delay in treatment. Patients are usually very indefinite about any detail in regard to activity of the lesion. However, for those from whom the information could be elicited, half had noted some change for more than six months. The second column indicates the delay, in 47 cases, from the time of excision of the primary focus to the time the patient was admitted to this series.

Patients appear reluctant or unable to give accurate information about early changes in a mole. However, about a third described an increase in size; a similar number stated that there was ulceration or that the lesion bled when injured slightly. A few described changes in pigmentation. In six of these 81 cases the primary lesion was never found, the first intimation of trouble having been the development of regional node metastasis. It is difficult to ascertain the role that injury may play in activating nevi to a malignant phase. In only two instances did patients suggest that repeated minor injury, such as shaving, might have some bearing on this change. Again five reported single major injuries, such as severe blows, but probably these incidents were all coincidental and had nothing at all to do with the development of a malignant status.

Table 3 shows the location of the primary lesions in cases in which they could be found. It should be noted that 40 of them were about the head and neck, including eight ocular primary lesions; 19 were on the upper extremity; 33 were on the trunk, including one in the anogenital area; 47 were on the lower extremity; in six cases a primary focus was never found. Table 4 indicates the size of the untreated lesions. When first seen, 36 had already been removed; 23 were less than, and 16 were more than two centimeters in mean diameter.

The total definitive treatment to the primary lesion, whether done by the author or elsewhere, is shown in Table 5. It is notable that 14 patients had

TABLE 2.—*Time from First Notice of Activity in Lesion to Beginning of Treatment*

	From "Activity" to First Treatment	From First Treatment to Time First Seen by Author
1 month or less	2	22
1 month to 6 months	10	8
6 months to 12 months	8	1
More than 1 year	7	16
Information not available	54	....
Previously untreated	....	34
Totals	81	81

TABLE 3.—*Locations of Primary Lesions*

Head and neck		40
Facio-scalp	32	
Ocular	8	
Upper extremity		19
Forearm and hand	4	
Arm	15	
Trunk		33
Lower extremity		47
Thigh	9	
Leg	19	
Foot	19	
Never found		6
Total		145

TABLE 4.—*Size of Primary Lesion (Mean Diameter)*

Less than 1.0 cm	10
1.0 cm. to 1.9 cm	13
2.0 cm. to 4.0 cm	14
More than 4.0 cm	2
Previously excised	36
Occult	6
Total	81

had only excisional biopsy and seven only cauterization. Most of these procedures had been done some time previously and enough time had elapsed to suggest that there would be no further trouble with the primary lesion. In five instances there was only an indefinite history of pigmented lesions having been "removed" several years before. In 50 cases

TABLE 5.—*Total Definitive Treatment to Primary Lesion*

Excision biopsy only	13
Cauterization only	7
"Removed" only	5
Primary radical excision	28
Secondary radical excision	22
No discoverable primary	6
Total	81

there was either primary or secondary radical excision of the original foci. In six instances, it was not possible to discover a primary site.

The treatment to the regional lymph nodes is summarized in Table 6. A total of 31 patients had radical node dissections either in continuity with the removal of the primary lesion or at the same time or at least within two months of the time of the original excision. The author now believes that "dissection in continuity," both anatomically and temporally, is the treatment of choice, but accepts the fact that a planned period of delay is still regarded as acceptable management. These 31 patients may all be regarded as having had node dissection without significant delay. Twenty-four of the 31 are still alive and well, free of any sign of recurrence. An additional 15 patients had node dissection after considerable delay for various reasons. Only six of them were alive and well at the time of this report. Thirty-five patients never had nodal dissections, or had only excision for biopsy.

The reasons for withholding or long delaying nodal treatment are indicated in Table 7. It was thought that the treatment of the primary neoplasm probably had been curative in 15 of the 35 cases in which nodal dissection had never been done. Included were one case of juvenile melanoma and the eight cases of orbital melanoma. Further treatment was refused by four patients, while in nine there was no justification for node dissection because the primary disease was never controlled. There were five examples of midline lesions in which it was impossible to determine which nodal area to dissect. Intercurrent disease in one patient and senility in another contraindicated operation. Among the cases of delayed nodal dissection, there were eight in which it was thought that the primary disease was cured by the original procedure; but in five cases this was not true, and the delay may well have been responsible for the death of all five patients. In the one instance in which there was long delay of nodal dissection because of the midline location of the melanoma, the disease was also lethal. The two patients who did not have nodal dissections because of age and intercurrent disease, respectively, also died of melanoma.

TABLE 6.—*Definitive Treatment of Regional Nodes*

Radical node dissection:	
In anatomic continuity with primary lesion	8
At same time primary treated but not in continuity	6
After planned delay of:	
2 months or less following treatment of primary	17
2 to 6 months after treatment of primary	3
7 to 12 months after treatment of primary	4
More than 12 months after treatment of primary	8
No definitive treatment, or biopsy only	35
Total	81

TABLE 7.—*Factors Producing Delay or Omission of Nodal Dissection*

		Delay from Primary Treatment to Dissection		
	No Dissection	2 to 6 Months	6 Months to 1 Year	Over 1 Year
Treatment of primary "cured" patient	15	1	1	6
Refused treatment	4	....	....	....
Primary disease never controlled	9	....	....	....
Midline lesion	5	....	1	....
Other	2	2	2	2
Totals	35	3	4	8

Many surgeons, pessimistic over the salvage being obtained for melanoma of the extremities, have been goaded by their poor results toward increasingly radical operation. Some investigators[5] have gone so far as to recommend routine amputation or disarticulation of the offending member, with nodal dissection in continuity, as the treatment of choice, particularly when regional metastasis is evident. I believe that the questionable improvement in salvage obtained by such mutilating procedures would be more than offset by the economic and functional loss to the entire group of patients involved and therefore have restricted the application of amputation to patients in whom recurrent disease has developed between the treated primary and the area of nodal dissection.

Obviously, if there is active disease between the treated primary and the previously dissected nodal area, no treatment other than amputation offers any hope for success. In three instances such a sequence of events made amputation of an extremity necessary; two of the patients are dead and one remains free of disease, indicating that in this situation the chance for cure is remote indeed. Further, no illusions are held as to "cure" in the other case although the patient had been free of disease for two years at the time of this report. This minuscule group of three cases might be cited as an argument for primary amputation as the treatment of choice for a melanoma of the extremities. On the other hand, of the 17 patients in whom both primary and regional

radical operation, concurrently or within two months, was done, 14 were alive and free of disease at the time of this report, two were dead, and one was alive with disease. Although there are not five-year figures, if a routine policy of amputation of the extremity had been applied to these patients, 17 extremities would have been amputated to date; but 14 were alive and free of disease without such drastic measures, and only two patients might have benefited from amputation.

PATHOLOGIC CLASSIFICATION

The group included only one case of "juvenile melanoma." This was in an eight-year-old child, and five years later she remained well. In two cases the lesions were described by the pathologist as "non-malignant" or "unable to metastasize." Because of such opinions, node dissections were not done and both patients died of generalized metastasis. Three lesions were stated to be amelanotic, while six primaries were never found despite excision of all neighboring nevi. All other lesions in the series were simply designated as melanoma, without reservation as to their fully malignant nature.

Of interest was the condition of the nodes at the time of the node dissection, indicated in Table 8. Of 23 patients who had "negative" nodes at the time of the dissection, 21 were alive and well at the time of this report. Of five with but a single node involved, two were known to be free of disease, one was dead and two were lost to follow-up. Of the 20 patients who had multiple node involvement, only three were free of disease at the time of this report. Such data imply that prompt treatment of melanoma (including nodal dissection) is probably of prime importance in control of the disease. One may state that if the nodes are "negative" at the time of nodal dissection, the patient has an excellent chance for cure; if the nodes are extensively involved the chance for cure is essentially nil.

It seems obvious that early treatment of the primary lesion and of the nodal areas is mandatory for successful management of this condition. Critics might state that if the nodes are not involved, there is no reason to remove them; that the cure rate would not be improved by node dissection. But one must keep in mind the highly malignant nature of melanoma, its almost total lack of cellular cohesiveness, and its infinite capacity for local invasion and lymphatic permeation. It seems probable, if not necessarily true, that occult lymphatic metastasis has occurred in every case of clinical melanoma. A pathological report of "nodes free of metastasis" may merely indicate that the few metastatic cells present have not been apprehended by the currently accepted

TABLE 8.—*Present Status of Patients with Reference to Nodes*

	Total Number	Free of Disease
Nodes negative	23	21
Single node positive	5*	2
Multiple nodes positive	20	3

*Including 1 dead, 2 lost to follow-up.

TABLE 9.—*Clinical Course After Completion of Treatment*

Remained free of disease	50
Lost	2
Recurrent disease between primary lesion and treated nodal area	3
Recurrent disease proximal to nodal area	1
Disseminated skin, or generalized metastasis	25
Total	81

laboratory methods of sampling such nodal tissue. Accepting this reasonable probability, a far more appropriate statement would appear to be this: If there is delay until the nodes appear to be clinically involved, nodal dissection is probably of little avail. This would indicate that every patient should have a regional node dissection as early as possible and before there is clinical evidence of metastasis in the suspect nodal area.

Table 9 is a summary of the subsequent clinical course of the 81 cases regarded as definitive in this study. Fifty remain free of disease and two were lost to follow-up. In three cases recurrent disease developed between the treated primary lesion and the area of radical node dissection, and amputation of the extremity was carried out. In one patient recurrent disease developed immediately proximal to the treated nodal area (obviously the nodal dissection was done too late) and amputation would have been of no benefit. Disseminated disease developed in 25 cases, apparently primarily blood-borne, and cure probably was impossible because of the mode of metastasis. At present there is no way of forestalling or dealing with blood-borne metastasis from this disease. The status of the definitive group at the time of this report is set forth in Table 10. While 32 of the patients were free of disease for periods less than three years, 18 were free for periods of from three to more than ten years; two were lost to follow-up, but had been free of disease when last seen; three were alive but had melanoma and 26 had died of melanoma. Eight of these already had generalized metastasis when first seen, and while they could not be excluded from the definitive group they were hopeless from a therapeutic standpoint.

A careful analysis (Table 11) of failures following treatment was undertaken to see what might have been done to avoid the fatality. In retrospect,

TABLE 10.—*Present Status of Definitive Group*

No evidence of disease:	
1 year or less	19
2 years	13
3 years	3
3 to 5 years	6
5 to 10 years	7
10 years	2
Lost to follow-up (without disease when last seen)	2
Alive with melanoma	3
Dead of melanoma	26
Total	81

TABLE 11.—*Analysis of Failures Following Treatment*

More aggressive treatment probably would not have favorably influenced the course of the disease because:	
(a) Incurable when first seen	6
(b) Died of blood-borne metastasis	2
Unfavorable outcome probably might have been altered by:	
(a) Less delay in treatment of primary lesion	3
(b) More radical treatment of primary lesion	5
(c) Less delay in doing node dissection	9
(d) Amputation with node dissection	3

six of the patients were undoubtedly incurable when first seen; an additional two died of blood-borne metastasis which had already occurred at the time of definitive treatment. In other words, there were eight cases in which more aggressive treatment would not have helped. But retrospective analysis of 20 other failures suggests that much might have have been done to improve the outcome. Among these, three would undoubtedly have benefited by less delay in treatment of the primary lesions; five by a more radical management of the primary lesion; and in nine cases there was excessive delay of node dissections, which probably contributed to the failure in the treatment program. There were three cases in which primary amputation might have brought about cure but in which this chance for cure was probably lost because of a more conservative approach. In summary, eight of the failures were probably unavoidable, but 20 of the patients might very well have been saved had less delay intervened in treatment of the primary lesion, if the original focus had been treated more radically, and if there had been less delay in doing node dissection.

DISCUSSION

Some uninformed dermatologists, and others who seem unable to accept or understand the almost uniformly lethal nature of melanoma, may persist in cauterizing or otherwise inadequately and/or meddlesomely trifling with this neoplasm. Fortunately for the patient, this approach is increasingly falling into discard. It would seem safe to state that, among those who have any appreciation of the malignant potential of melanoma, there is uniform agreement that prompt and radical surgical excision of the primary lesion is in order. There would be considerably less unanimity in regard to management of the regional node problem. Yet the mounting evidence points in but one direction.

DeWeese[2] summarized the experience in a university hospital before 1948 where the practice had been to radically excise the primary lesion but to withhold node dissection until metastasis was clinically evident. He reported that only 7.9 per cent of patients so managed remained free of recurrence beyond the five-year period and concluded the poor results achieved by late dissection of clinically involved nodes made a more aggressive approach to the problem necessary. Lund and Ihnen,[4] reporting on a comparable group similarly managed, said that but one of 19 patients operated on after nodes were apparently involved survived five years. They conclude that "prophylactic" dissection should be done.

While the desirability of attacking melanoma radically by wide surgical excision and regional lymph node dissection was indicated as early as 1907 by Handley,[3] acceptance has been slow. Pack and associates[7] emphasized the application of the principle of excision of the primary lesion and dissection of nodes in anatomic continuity, citing decided increases in salvage where such operations were done. While this procedure represents the acme in surgical management of any form of cancer, too often it is not applicable to the management of melanoma, because of the anatomic location of the primary focus at a great distance from or equidistant between nodal groups. This has made the application of "discontinuous dissection" of the primary lesion and nodal areas necessary in many cases—that is, excision of the two areas in anatomic discontinuity, and sometimes with a lapse of time between dissections.

Some investigators suggested that a period should elapse between the surgical excision of the primary and the regional nodal dissection to permit "filtering out" by the nodes of transient cells in the lymphatics intervening between the primary and the nodal groups to be dissected. Suggestions as to the time that should be permitted have varied from six weeks in cases without palpable nodes[2] to from one to two weeks. While it is undoubtedly true that the metastatic cell will pursue a dilatory and lagging course to the regional nodes if these structures themselves and the afferent lymphatic channels are blocked by tumor, this is the situation where there is clinical evidence of metastatic involvement of the nodes. Indeed, repeated failures of lymph nodes blocked with tumor to collect colloidal isotopes introduced into areas drained by their afferent lymphatic channels suggests that particulate matter in

lymphatic systems so involved may *never* reach the nodes. Additional evidence indicates that material passes quickly along unobstructed lymphatics and lodges in the regional node group in a matter of minutes, probably in much less time than is required to surgically ablate the primary site. Weinberg and Greaney[9] reported satisfactory impregnation of unblocked regional lymph nodes by injected supravital dyes in 15 minutes, and said that in 30 minutes successive echelons of nodes may be visualized by this technique. Because of the rapidity of this lymphatic transmission, there appears to be little validity in waiting for a prolonged "filtering out" period in the absence of clinical evidence of involvement; and if "dissection in continuity" cannot be achieved for anatomic reasons, it should at least be possible to effect the surgical management of such situations in continuity with reference to time even though not anatomically.

The five-year salvage rate (Taylor and Nathanson[8]) of but 2.6 per cent when there was nodal involvement at the time of surgical treatment is discouraging but significant. In contrast are reports of over-all five-year salvage rates of 38 per cent[1] and 40 per cent[6] when these more aggressive surgical approaches were employed. These are compelling reasons for the application of the principle of "prophylactic" node dissection for melanoma when possible.

2009 Wilshire Boulevard, Los Angeles 57.

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